Conferences and Reviews

The Skin as an Immune Organ

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As a protective interface between internal organs and the environment, the skin encounters a host of toxins, pathogenic organisms, and physical stresses. To combat these attacks on the cutaneous microenvironment, the skin functions as more than a physical barrier: it is an active immune organ. Immune responses in the skin involve an armamentarium of immune-competent cells and soluble biologic response modifiers including cytokines. Traversed by a network of lymphatic and blood vessels, the dermis contains most of the lymphocytes in the skin, other migrant leukocytes, mast cells, and tissue macrophages. Although the epidermis has no direct access to the blood or lymphatic circulation, it is equipped with immune-competent cells: Langerhans cells, the macrophage-like antigen-presenting cells of the epidermis; keratinocytes, epithelial cells with immune properties; dendritic epidermal T lymphocytes, resident cells that may serve as a primitive T-cell immune surveillance system; epidermotropic lymphocytes, migrants from vessels in the dermis; and melanocytes, epidermal pigment cells with immune properties. Although the components of the epidermis and dermis work in concert to execute immune responses in the skin, for purposes of this review, we focus on the cells and cytokines of the epidermal immunologic unit, the frontline of immune protection against environmental toxins and microbes.

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Cutaneous immune responses involve the coordinated actions of epidermal and dermal cells along with the intricate network of cytokines. Streilein was among the first to propose a branch of the immune system specialized to provide cutaneous immunity; in 1978, he introduced the concept of skin-associated lymphoid tissues or "SALT," analogous to the gut, bronchial, or conjunctival-associated lymphoid tissues.[1] Skin-associated lymphoid tissue is an integrated system in which resident epidermal cells, keratinocytes and Langerhans cells, as well as migrant epidermotropic lymphocytes and draining regional lymph nodes, work in concert to provide the skin with immune protection against external environmental toxins, infections, and the development of cutaneous neoplasms.

Together the cells in the epidermis also serve as a vast reservoir of soluble biologic response modifiers. The cytokines produced in the epidermis allow the skin to recruit and activate a wide range of inflammatory cells. Many of these cytokines are released from the epidermis whenever the cutaneous barrier is compromised, whether by direct trauma, infections, allergens, or toxins. The local release of these cytokines and the systemic absorption through the superficial vascular plexus of the upper dermis serve as an early signal to the host immune system that the external barrier (skin) has been disrupted. In this way, the immune system can be activated, mobilized, and directed to the site of cutaneous injury and the source of secreted cytokines.*

Cellular Components of the Epidermal Immune Unit

Langerhans Cells—Epidermal Antigen-Presenting Cells

In 1868 Paul Langerhans, a medical student interested in the anatomy of cutaneous nerves, inoculated gold into human skin and discovered a population of dendritic cells in the epidermis.[2] Although originally thought to represent intraepidermal neural receptors, Langerhans cells are now recognized as the major antigen-presenting cells of the skin and play a key role as the peripheral component of the immune system. Langerhans cells are one of a large family of class II major histocompatibility complex (MHC)-bearing dendritic cells critical to antigen processing and presentation to specific T lymphocytes. Langerhans cells contain intracytoplasmic "tennis racket-shaped" organelles called Birbeck granules that appear to result from the internalization of class II MHC cell-surface molecules; the precise role of these unique granules in anti-

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ABBREVIATIONS USED IN TEXT

CLA = cutaneous leukocyte-associated antigen
ELAM = endothelial cell-leukocyte adhesion molecules
ICAM = intercellular adhesion molecule
IFN = interferon
Ig = immunoglobulin
LFA = lymphocyte function-associated antigen
MHC = major histocompatibility complex
TNF = tumor necrosis factor
V = variable gene segment of the T cell-receptor gene

gen-processing, presentation, or both is unclear.[3] These cells are capable of phagocytosis, although their efficiency at this feat is less than that of macrophages and even keratinocytes. Langerhans cells have receptors for the Fc component of immunoglobulin (Ig) G and IgE and the third component of complement (C3). These receptors may facilitate phagocytosis of antibody and complement-coated particles.[4,5]

Derived from the monocytic lineage of the bone marrow, Langerhans cells migrate to the skin to make up 2% to 4% of epidermal cells, with most taking residence in the suprabasal regions of the epidermis; a few cells may be found in the dermis, draining lymph nodes, and in the thymus.[4] In the epidermis, their long dendritic processes intercalate between keratinocytes, and although there is no evidence of physical or functional contact between dendrites, they appear to form an "immunologic net" parallel to the skin surface, efficiently trapping antigenic molecules.

In normal, noninflamed epidermis, Langerhans cells are the only cells that express a substantial level of class II MHC antigens (HLA-DP, -DR, -DQ in humans; Ia and Ie in the murine system).[6] These surface molecules are required for the stimulation of T cell-dependent immune responses. Langerhans cells play a two-tiered antigen-presenting role in the peripheral immune system: they present antigen in the context of class II MHC molecules to naive T cells in the induction of cell-mediated immunity and to memory and effector T cells in the expression of cutaneous immune responses.[7] They are critical to cutaneous antigen-specific syngeneic and allogeneic T-cell activation and the generation of epidermal cell-induced cytotoxic T cell reactions.[4,8] They are required for the induction of cutaneous delayed-type hypersensitivity responses[9] and are critical to epidermal allosensitization such as graft-versus-host reactions.[4,8] There is experimental evidence that during the sensitization or induction of a T cell-mediated immune response, Langerhans cells process exogenous antigen and form complexes with cell surface class II MHC molecules in a manner similar to that of tissue macrophages. Antigen-bearing Langerhans cells undergo certain phenotypic changes and migrate through dermal lymphatics to regional lymph nodes where they become more like the dendritic cells of lymph nodes, stimulating specific naive or primed T lymphocytes to proliferate and differentiate. The antigenic signal is transduced into an effector signal by specifically sensitized cells or antibodies; these immune effectors may then leave the lymph node and circulate in the bloodstream to the original site of antigenic stimulation, interact with specific antigen-bearing Langerhans cells, and execute an immune response. If at the time of the initial antigenic stimulation the appropriate antigen-specific lymphocytes are already in the skin, antigen recognition during the inductive phase of the immune response may take place entirely within the skin.[10]

The efficiency of these cells to function as antigen-presenting cells depends not only on the expression of cell surface class II MHC molecules but also on membrane adhesion molecules. Cellular adhesion molecules allow direct physical contact between Langerhans cells and T cells, thus facilitating their interactions and T-cell activation. Langerhans cells in vitro express adhesion molecules, such as intercellular adhesion molecule (ICAM)-1 (which is identical to CD54) and lymphocyte function-associated antigen (LFA)-3, both of which are glycoproteins of the immunoglobulin gene superfamily. Intercellular adhesion molecule-1 is the ligand for LFA-1, an integrin that is present on the surface of most hematopoietic cells and antigen-presenting cells, and LFA-3 is the ligand for CD2 (which is identical to LFA-2), a glycoprotein of the immunoglobulin gene superfamily that is present on T lymphocytes.[11,12]

Cytokines such as interleukin-1 and tumor necrosis factor (TNF)α that are produced by keratinocytes may increase class II MHC and adhesion molecule expression on Langerhans cells, thus augmenting their efficiency as antigen-presenting cells.[13] Furthermore, Langerhans cells may themselves modulate immune responses in the skin through the secretion of soluble mediators such as interleukin-1β, which can act in an autocrine and paracrine manner to promote immune responses in the skin.[14] In addition, preliminary studies suggest that Langerhans cells may express messenger RNA for interleukin-6 and macrophage inflammatory protein-1α.[5] Thus, these cells represent a key component of the host immune system responsible for initiating cutaneous cellular immune responses.

Keratinocytes—Immune-Competent Epithelial Cells

Over the past few years, the revelation that keratinocytes are immunologically active cells has reinforced the concept that the skin is an active immune organ.[1] Accounting for greater than 90% of epidermal cells, keratinocytes not only create a complex physical barrier to environmental agents but also serve as accessory cells in cutaneous immune responses. Keratinocytes may play a role in initiating cell-mediated immune responses in the skin by releasing cytokines and expressing cellular adhesion molecules to facilitate the movement of immune-competent cells.

In 1976 Edelson, who was studying cutaneous T-cell lymphoma, a disease characterized by epidermal infiltration by malignant T-helper cells, became one of the first to suggest that epidermal cells may influence T-lymphocyte migration and proliferation.[15] In 1981 Rubenfeld and

co-workers observed that epidermal cell cultures produce soluble substances that induce lymphocyte differentiation,[16] and a year later, Chu and associates discovered a keratinocyte-derived factor similar to thymopoietin.[17] During this period, Luger and colleagues, along with Sauder and co-workers, discovered and further characterized a keratinocyte-derived cytokine that was initially named epidermal cell-derived thymocyte activating factor and is now known to be identical to interleukin-1.[18-20]

It is now well established that keratinocytes constitutively synthesize the two subtypes of interleukin-1: both interleukin-1α and, to a lesser extent, interleukin-1β.[20,21] Keratinocytes lack the ability to export interleukin-1 under normal conditions but may be activated—by other cytokines—to secrete interleukin-1 or may undergo direct cell injury to allow the release of this cytokine. They may thus serve as a vast reservoir of this protein factor, synthesizing and storing the cytokine until the appropriate stimulus induces interleukin-1 secretion to initiate local and systemic inflammatory responses.[22] Interleukin-1 is a pleotropic cytokine with a broad spectrum of biologic effects, including inducing thymocyte proliferation, activating T and B cells, amplifying the immunostimulatory potential of dendritic cells, promoting monocytic cytotoxic activity against tumor cells, stimulating fibroblast mitogenesis and collagen synthesis, producing hepatic acute-phase reactants, and inducing fever. Target cells of interleukin-1 include keratinocytes, T lymphocytes, neutrophils, macrophages, fibroblasts, and smooth muscle cells. Through autocrine and paracrine actions, interleukin-1 may augment the expression of its receptors on target cells and induce keratinocytes to synthesize and secrete interleukin-1 and other cytokines. It is now recognized that "activated" keratinocytes produce at least 15 biologic response modifiers, and the list of mediators continues to grow.[22,23] This array of cytokines can mediate the wide variety of inflammatory responses observed in the skin.

In addition to cytokine production, keratinocytes may directly participate in cell-mediated immune responses by the expression of class II MHC molecules. In normal, noninflamed epidermis, keratinocytes have only class I MHC antigens on their surface and do not express class II MHC antigens (HLA-DP, -DQ, and -DR in humans). In inflamed skin, however, infiltrating T lymphocytes secrete interferon γ (IFN-γ), which is capable of activating keratinocytes to transiently express class II MHC antigens (DR).[24] The role of class II antigen-bearing keratinocytes in cutaneous immune responses has not been established. Although these activated cells do not appear capable of presenting antigen to naive T cells, some studies have suggested that they may activate memory and effector T cells. Other data suggest, however, that class II MHC-bearing keratinocytes provide signals that specifically inhibit cell-mediated immune responses in the skin.[25]

Activated keratinocytes may also influence the movement of immune-competent cells and effector cells into the skin by the expression of specific adhesion molecules such as intercellular adhesion molecule (ICAM)-1. Although keratinocytes do not constitutively express ICAM-1 (as do Langerhans cells and human dermal microvascular endothelial cells), they may be induced to express the ICAM-1 molecule by secreted IFN-γ and TNFα.[12,26] T lymphocytes that express cell surface LFA-1 may adhere to cells expressing ICAM-1 such as keratinocytes specifically by LFA-1–ICAM-1 conjugate formation. This interaction may be important in recruiting and moving immune cells to the point of antigenic stimulation or skin injury.[12,27] For example, during allergic contact hypersensitivity reactions, ICAM-1 expression on keratinocytes temporally correlates with the dermal infiltration of mononuclear cells and the development of clinical dermatitis.[28] Keratinocyte ICAM-1 expression is also increased in psoriatic skin lesions and correlates with a dense mononuclear infiltrate; treatment with methoxsalen (8-methoxypsoralen) and ultraviolet A results in a pronounced decrease in ICAM-1 expression on keratinocytes that parallels a reduction in the mononuclear dermal infiltrate and clinical improvement.[29] Keratinocyte ICAM-1 expression in juxtaposition with epidermotropic LFA-1-expressing T lymphocytes has been described in a number of other inflammatory dermatoses, such as lichen planus, and in cutaneous cancers, namely the early stages of cutaneous T-cell lymphoma, also known as mycosis fungoides.[30] In addition, under the stimulation of IFNγ, human keratinocytes may secrete soluble ICAM-1 molecules that can bind to LFA-1 and possibly competitively block LFA-1-mediated cellular interactions. Because some malignant keratinocytic lines have been shown to constitutively synthesize soluble ICAM-1 (without cytokine stimulation), some have speculated that soluble ICAM-1 may provide a mechanism by which these neoplastic cells may escape from immunologic cytotoxicity.[31]

Dendritic Epidermal T Cells—Specialized Resident Epithelial T Cells

In 1983 Tschachler and Bergstresser and associates independently described a population of dendritic epidermal T cells that express Thy-1 cell surface glycoprotein but lack class II MHC antigen.[32,33] Also known as Thy-1$^+$ dendritic epidermal cells, dendritic epidermal T cells are a unique subset of epidermotropic bone marrow-derived cells that have been best defined in mice. To date, a precise equivalent in human skin has not been described. Residing in the basal layer of the epidermis as a relatively sessile, dendritic population of cells distinct from melanocytes and Langerhans cells, dendritic epidermal T cells make up 0.8% to 2% of murine epidermal cells.[34,35]

The phenotypic features of dendritic epidermal T cells are intriguing: they share with immature thymocytes the Thy-1 alloantigen, CD45, and CD3 antigens as well as the neutral glycolipid asialo-Gm-1 antigen, which is a marker for natural killer cells but may also be present on thymocytes and certain peripheral T cells.[32,33,35,36] Dendritic epidermal T cells lack mature peripheral T-cell markers such as CD5 and CD4, and most of these cells also lack CD8 antigens.[32,37] Like immature thymocytes, the CD3 antigens of dendritic epidermal T cells are predominantly associ-

ated with T-cell receptor γ/δ heterodimers rather than the α/β heterodimers that are present on most peripheral T cells.[34,38] Antigen recognition by dendritic epidermal T cells is not restricted by conventional polymorphic class I or class II MHC molecules but instead appears to be restricted by relatively nonpolymorphic self-MHC-like molecules of the class Ib MHC type.[35] In addition, dendritic epidermal T cells are characterized by limited T cell-receptor diversity: the cells selectively express variable (*V*) gene segments and display restricted γ/δ pairing such that the epitopes of dendritic epidermal T-cell receptors in the epidermis are predominantly *V*γ3 and *V*δ1.[34,39] The limited expression of *V*γ and *V*δ genes, the lack of CD4 and CD8 antigens, and the early appearance of γ/δ cells during murine ontogeny suggest that these cells may represent a phylogenetically "primitive" immune defense system.[35]

The specific function of this unique subset of epidermal T cells has eluded investigators. These epidermal T cells may participate in cutaneous immune surveillance, possibly by cytotoxic activities against foreign or altered-self target cells. In vitro, interleukin-2–stimulated dendritic epidermal T cells gain natural killer-like cell properties and mediate non-MHC-directed cytotoxicity.[36] These epidermal T cells may also secrete immunologic cytokines such as interleukin-2.[35,39] Some studies suggest that they may also play a role in the induction of tolerance. Hapten-conjugated dendritic epidermal T cells injected into a mouse footpad do not elicit contact hypersensitivity but instead induce antigen-specific tolerance that does not require the recognition of polymorphic self-MHC molecules. Because of the cytotoxic potential of these cells, some investigators have suggested that hapten-conjugated dendritic epidermal T cells may bind to T-helper cells (which express a hapten-specific receptor) and induce tolerance by killing these T-helper cells in a non-MHC-restricted manner.[40] Other studies, however, have not uniformly demonstrated the induction of tolerance after the subcutaneous administration of hapten-conjugated epidermal T cells, possibly because of different study designs and techniques.[41]

Another interesting theory regarding dendritic epidermal T-cell function takes into consideration the limited diversity of their γ/δ receptors, which, as mentioned, suggests a narrow range of ligands. Asarnow and co-workers have proposed that the mammalian heat-shock proteins may serve as a common ligand for these cells.[38] Heat-shock proteins are a highly conserved family of molecules that can be expressed by cells after a variety of insults, such as heat, hypoxia, ultraviolet radiation, γ-irradiation, viral infection, and malignant transformation.[35] Furthermore, cells infected with various species of mycobacteria can produce proteins that are homologous to mammalian heat-shock proteins.[35,42] Thus, it is possible that the relatively homogeneous receptors of dendritic epidermal T cells recognize and respond to a number of physical and chemical stresses that have been transformed into a common antigenic stimulus, that is, heat-shock (or related) proteins.

In humans, cells equivalent to murine epidermal T cells have not been found, although some distinct subsets of T lymphocytes share some of their features. These subsets include nondendritic γ/δ T cells and "double-negative" ($CD4^-CD8^-$) α/β T cells. Although most T lymphocytes in humans express the α/β-antigen receptor, 1% to 15% of intraepidermal and dermal T lymphocytes express the γ/δ-antigen receptor. Like murine dendritic epidermal T cells, human γ/δ T cells usually lack the CD4 and CD8 antigens and are capable of a non-MHC-restricted recognition of tumor targets. Human γ/δ T cells also recognize some specific antigens such as heat-shock proteins and mycobacterial antigens.[34,43]

Similar to most human γ/δ T cells and murine dendritic epidermal T cells, a few α/β T cells described in both humans and mice lack both CD4 and CD8 antigens (in contrast to the vast majority of α/β T cells that express either the CD4 or CD8 antigens). Like murine epidermal T cells, these "double-negative" α/β cells display non-MHC-restricted cytotoxicity against several tumor targets. Double-negative α/β T cells in mice display restricted expression of the *V*b-gene region; further studies are needed to characterize the degree of T cell-receptor diversity in human α/β $CD4^-CD8^-$ T cells.[44]

Unlike murine dendritic epidermal T cells, human γ/δ T cells and double-negative α/β T cells lack a dendritic structure and do not appear to selectively home to epithelial tissues. Nevertheless, the shared phenotypic features with epidermal T cells and the possible functional similarities are intriguing. These unique T-cell subsets, functioning in a manner distinct from MHC-restricted immune pathways, may provide an early defense network against a variety of insults, such as mycobacterial and other infections, tumor cells, and so on, by a common antigenic stimulus, such as heat-shock proteins.

Epidermotropic T Lymphocytes—Circulating T Cells That Home to the Epidermis

Circulating skin-homing lymphocytes are crucial to the initiation and execution of cutaneous immune responses. In normal human skin, all extravascular lymphocytes are of the T-cell type. Most of these T cells express the α/β-antigen receptor in contrast to the previously discussed γ/δ receptors expressed on murine dendritic epidermal T cells. The perivascular or periadnexal areas in the dermis contain 90% of the cutaneous T lymphocytes. These dermal T lymphocytes comprise an approximately equal number of $CD4^+$ inducer and $CD8^+$ suppressor or cytotoxic lymphocytes; of the $CD4^+$ T cells, most are $CD4^+$ $4B4^+$ helper or inducer cells, whereas less than 5% are $CD4^+$ $2H4^+$ suppressor-inducer T lymphocytes. The vast majority of dermal lymphocytes are in the activated state (express HLA-DR and interleukin-2 receptors). Less than 2% of T lymphocytes in the skin are within the epidermis where they make up 0.16% of epidermal cells; virtually all intraepidermal T lymphocytes are $CD2^+$, $CD3^+$, $CD8^+$ suppressor-cytotoxic T lymphocytes.[45] That the composition of the lymphocytic infiltrates within the skin does not mirror their concentrations in the peripheral

bloodstream supports the concept of nonrandom migration of lymphocytes into the skin and T-cell "homing."[1]

Intercellular adhesion molecules expressed on dermal endothelial cells may mediate leukocyte adhesion, migration through vessel walls, and trafficking into the dermis and epidermis. T lymphocytes can adhere to both endothelial cells and keratinocytes specifically by LFA-1–ICAM-1 conjugate formation. Endothelial cells constitutively express low levels of ICAM-1 and can be induced to express increased levels of ICAM-1 by interleukin-1, TNFα, and IFN-γ.[46,47] As described earlier, IFN-γ and TNFα may also induce ICAM-1 expression on keratinocytes, and T-cell migration to the epidermis may be inhibited by antibodies directed against LFA-1 and ICAM-1.[12,26,48]

Endothelial cell-leukocyte adhesion molecule (ELAM)-1 and cutaneous lymphocyte-associated antigen may compose another receptor-ligand pair that directs the movement of T lymphocytes to the skin.[49,50] Endothelial cell-leukocyte adhesion molecule-1 is a member of the "LEC-CAM" or "selectin" family of cell adhesion molecules. Although it may be present on inflamed endothelial cells of nearly any tissue, its expression is particularly prominent on inflamed endothelial cells of the skin.[49] Soluble mediators of inflammation such as TNFα may increase the expression of ELAM-1 on endothelial cells.[51] Neutrophils bear the sialylated Lewis x determinant, which can serve as a ligand for ELAM-1; the ligand on T cells has not yet been identified but may be the cutaneous lymphocyte-associated antigen (CLA). (This is not to be confused with the common leukocyte antigen, CD45, a marker present on a specific subset of memory T cells.[49,50,52]) Some investigators have proposed that ELAM-1 may serve as a "skin vascular addressin," a tissue-selective endothelial cell adhesion molecule for skin-homing memory T cells.[49,50]

During the efferent phase of cutaneous immune responses, memory and effector T cells (generated in the regional lymph nodes that drain the original site of antigen exposure) circulate in the bloodstream; meanwhile, at the site of antigenic stimulation, cytokines, such as IFN-γ and TNFα, are released and increase ICAM-1 and ELAM-1 expression on endothelial cells. These adhesion molecules serve as recognition signals for leukocytes that express LFA-1, CLA, or both. Through conjugate formation between LFA-1 and ICAM-1 and CLA and ELAM-1, memory and effector cells may be efficiently targeted to the site of antigen exposure or skin injury.

Melanocytes—Epidermal Pigment Cells With Immune Properties

Although melanocytes have been traditionally considered to have no immunologic role, recent findings suggest that these cells may contribute to the immune function of the epidermis by secreting biologic response modifiers. Melanocytes represent 2% to 5% of epidermal cells; the number of melanocytes varies from person to person and in different anatomic sites of the same person. Like Langerhans cells, they possess numerous dendritic processes and are strategically placed in the lower epidermis, close to the dermis, where they may play important roles in immune responses.[53]

Melanocytes produce a number of cytokines that may mediate inflammation in the epidermis and dermis. Melanocytes constitutively produce interleukins-1, -3, and -6, granulocyte-macrophage colony-stimulating factor, TNFα, and transforming growth factor β[54-58] and, after exposure to specific cytokines or neuropeptides, can increase the production of these cytokines and secrete interleukin-8 and monocyte chemotactic and activating factor.[53] Cultured melanocytes may produce both interleukin-1α and β and, unlike keratinocytes, contain a convertase enzyme that transforms the inactive 33-kd interleukin-1β to the active 17-kd product. Some investigators have suggested that the melanocyte-derived interleukin-1β convertase may act on the 33-kd interleukin-1β produced by keratinocytes to create an active mediator.[54,55]

Cytokines may have other autocrine and paracrine actions on melanocytes, influencing their growth, migration, enzymatic (tyrosinase) activity, and their expression of adhesion molecules, which are critical to cell-cell interactions. Although human melanocytes do not constitutively express adhesion molecules, IFN-γ, TNFα and β, interleukins-1α, -6, and -7 may induce ICAM-1 expression on melanocytes (depending on culture conditions).[59,60] Future studies will elucidate the nature of the interactions between melanocytes and other cells of the immune system.

Summary

It is clear that the epidermis can function as an immunologic tissue. This is critically important to its function as a barrier to external toxins and microbes. In this review, we have focused on the major immune-competent cells of the epidermis. To recapitulate, one of the first cells to encounter toxins or antigens in the skin are the macrophage-like Langerhans cells. As the major antigen-presenting cells of the epidermis, Langerhans cells play a critical role in both the afferent and efferent limbs of the cutaneous immune system. Parenchymal cells, most of which are keratinocytes, serve as accessory cells in cutaneous immune responses. As a reservoir of preformed interleukin-1, keratinocytes may function as an early warning system, releasing this cytokine after cellular injury or cytokine activation. Interleukin-1 may then exert a multitude of local and systemic effects, acting directly on cells and indirectly through the modulation of cytokine production. Moreover, it acts on all of the key components of the cutaneous immune system: interleukin-1 increases cytokine production of keratinocytes and induces class II MHC antigen and ICAM-1 expression on keratinocytes; it augments the immunostimulatory potential of Langerhans cells by enhancing their expression of class II MHC antigen; it also increases the expression of adhesion molecules on dermal endothelial cells, further facilitating leukocyte trafficking into the skin; furthermore, interleukin-1 is chemotactic for T lymphocytes and promotes their production of and respon-

siveness to cytokines. In murine epidermis, dendritic epidermal T cells may represent a primitive immune surveillance system of epithelial tissues. Another possible component of the cutaneous immune system is melanocytes, which may serve as accessory cells by secreting soluble mediators of inflammation.

Although we have focused on the epidermal immune unit, we recognize that the epidermis interacts substantially with the underlying dermis, which is populated with immune-competent cells and soluble inflammatory mediators. Recent advances in immunodermatology have illuminated the complexity of this amazingly effective and efficient physical and immunologically active barrier. With the powerful tools of molecular biology available, new dimensions are continually being added to these concepts as we expand our understanding of the skin as an immune organ and explore new therapies for cutaneous disease.

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TRIPLE BYPASS

I hide my face though cybernetic dreams
surround me like sentinels on parade.

Technical hobgoblins call it pericardium
for me the gates of heaven unveil and I

divine celestial majesty pulsating
with rhythmic hymns of life and glory.

If God lives he lives below the sixth rib among
conical truths echoing the heckles of a human heart.

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